

Peer Review File

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Reviewer A

This is an interesting case of metastatic SCNEC in a very young patient. Although the authors have not provided any novel findings, the rarity of the disease is notable for case study. I believe this work would be enhanced with a literature review of the cases of metastatic SCNEC to the breast from various sites and potential pitfalls for clinicians.

Response to reviewer:

- Thank you very much for your valuable comments.

Comment 1: Page 3 Line 5: Please indicate rarity in percentages or number of cases.

Reply 1:

- Thank you very much for your valuable comments.
- SCNEC is rare and accounts for less than 2% of all invasive cervical malignancies.
- We have incorporated this information into the manuscript in accordance with your insightful suggestion.

Changes in the text:

Page 3 [line 4-5](#)

SCNEC of the cervix is rare, representing less than 2% of all cases of cervical cancer and aggressive compared with squamous cell carcinoma and adenocarcinoma subtypes.

Comment 2: Page 3 Line 7-8: Please indicate rarity in percentages or number of cases, please indicate how common metastasis to each site is.

Reply 2:

- Thank you very much for your valuable comments.
- From retrospective study that obtain data from the surveillance epidemiology and end results (SEER) database from 2000 to 2018 of metastatic neuroendocrine carcinoma of the cervix. That showed single-site metastases accounted for 55.6% of the cases, with liver metastases being the most common site of metastasis (20.4%), followed by lung (19.7%) and bone (13.4%) metastases. 44.4% of patients had multi-organ metastases.
- We have incorporated this information into the manuscript in accordance with your insightful suggestion.

Changes in the text:

Page 3 [line 7-8](#)

Common sites of metastasis are the [liver \(20.4%\), lung \(19.7%\) and bone \(13.4%\)](#). [44.4% of patients had multi-organ metastases. Metastatic SCNEC to the breast is extremely rare.](#)

(Reference: Li Q, Yu J, Yi H and Lan Q (2022) Distant Organ Metastasis Patterns and Prognosis of Neuroendocrine Cervical Carcinoma: A Population-Based Retrospective Study. Front. Endocrinol. 13:924414.)

Comment 3: Page 3 Line 14: the current iteration is cumbersome, would suggest breast cancer “due to” the different therapeutic options.

Reply 3:

- I greatly appreciate your valuable suggestion and am sincerely grateful for it.
- We have revised our text according to your suggestions.

Changes in the text: Page 3 Line 12-14

Although primary breast cancers are more common, histopathological confirmation is necessary to differentiate metastatic extramammary cancer from metastatic primary breast cancer [due to](#) the different therapeutic options for the two conditions.

Comment 4: Page 4 Did the patient have any relevant past medical history?

Was the case pure SCNEC or were there squamous or adenocarcinoma components as well?

Reply 4:

- Thank you very much for your valuable comments.
- The patient had no underlying medical disease.
- In this case, the tumor cells are diffusely positive for synaptophysin and chromogranin, which are neuroendocrine markers. The diagnosis was compatible with pure small cell carcinoma from the biopsy specimen.
- We have incorporated this information into the manuscript in accordance with your insightful suggestion.

Changes in the text:

Page 4 [line 3](#)

We added “[She didn’t have any underlying medical disease](#)”.

Page 4 [line 19](#)

which showed [pure small cell carcinoma without any squamous or adenocarcinoma component](#).

Comment 5: Page 4 Line 4: Please clarify that she was diagnosed with SCNEC cervical cancer, indicate stage at diagnosis. Did the patient not have a trachelectomy or hysterectomy? Was staging done?

Reply 5:

- Thank you very much for your valuable comments.
- Because the first gynecologist misses diagnosis SCNEC cervical cancer. She was diagnosis as stage IIB squamous cell carcinoma of cervix, from cervical biopsy specimen at rural hospital. In FIGO stage IIB and above are not usually treated with hysterectomy, as delineated in the Guidelines. The patient was a young woman and preferred the ovarian preservation. So that the patient was treated by laparoscopic ovarian transposition with bilateral salpingectomy followed by definitive concurrent chemoradiation. She didn’t undergo trachelectomy or hysterectomy. But after she was re-visited with breast masses. We retrospectively reviewed the tissue blocks and performed immunostains of the cervical mass from the rural hospital, which showed the same morphology and immunohistochemistry of cervical masses compared with breast masses.
- We have incorporated this information into the manuscript in accordance with your insightful suggestion.

Changes in the text:

Case Presentation Page 4 [Line 3-5](#)

She had been diagnosed with [stage IIB](#) cervical cancer 1 year earlier [and was treated as squamous cell carcinoma of cervix](#). [There was a result of cervical biopsy specimen from a rural hospital](#). So, she didn’t

undergo trachelectomy or hysterectomy. But she was treated by laparoscopic ovarian transposition with bilateral salpingectomy followed by definitive concurrent chemoradiation.

Page 4 [Line 18](#)

We retrospectively reviewed the tissue blocks and performed immunostains of the cervical mass, which showed pure small cell carcinoma without any squamous or adenocarcinoma component and positive for synaptophysin, chromogranin, AE1/AE3, PAX8, p16. There were the same histomorphological and immunohistochemical results as those of the breast masses.

Comment 6: [Page 4 Line 17](#): Paired-box gene 8 (PAX8)

Reply 6:

- Thank you very much for your valuable comments.
- We have revised these according to your suggestions.

Changes in the text:

Page 4 [Line 17](#) “Paired-box gene 8 (PAX8)”

Page 6 [Line 13](#) “PAX8”

Comment 7: [Page 4 Line 18/19](#): Please include an additional figure to show histological similarity to primary tumor. What markers were used to diagnose the primary tumor. Discuss if they were concordant.

Reply 7:

- Thank you very much for your valuable comments.
- We have improved the quality for Figure 2, showing the similar histomorphology between primary cervical tumors and metastatic tumors at breast.
- In this patient, firstly presented with vaginal bleeding and cervical mass. After retrospectively reviewing the tissue blocks and performing immunostains, the tumor cells showed small-shaped nuclei with nuclear molding. The tumor cells were diffusely positive for synaptophysin, chromogranin, also positive for PAX8 and block-type staining of p16. PAX8 immunostaining plays an essential role as an adjunct tool in diagnosing cervical cancer and p16 is a surrogate marker for high-risk HPV infection. This was compatible with small cell carcinoma of cervix.
- In the latest visit that present with breast masses, the breast histomorphology was similar to the cervix. The immunohistochemical study revealed the same profiles as the cervix (positive for chromogranin, synaptophysin, PAX8 and p16). Due to PAX8 positivity and negative result for GCDFP 15, one of specific and sensitive markers in breast cancer. So that primary breast cancer is unlikely. The diagnosis was compatible with metastatic small cell carcinoma from cervical origin to the breast that correlates with clinical history.
- We have incorporated this information into the manuscript in accordance with your insightful suggestion and discussion in Page6 line 7-18.

Changes in the text:

Case Presentation Page 4 [Line 14-20](#)

Core needle biopsies of both left breast masses and the left supraclavicular lymph node were performed and revealed small round cell tumors with papillary features on microscopic examination. These tumor cells were positive for pan-cytokeratin (AE1/AE3), synaptophysin, chromogranin, Paired-box gene 8 (PAX8), and p16 (Figure 2) and negative for CK5/6, gross cystic disease fluid protein-15, estrogen receptor, and progesterone receptor. We retrospectively reviewed the tissue blocks and performed immunostains of the cervical mass, which showed pure small cell carcinoma without any

squamous or adenocarcinoma component and positive for synaptophysin, chromogranin, AE1/AE3, PAX8, p16. There were the same histomorphological and immunohistochemical results as those of the breast masses. These findings were consistent with metastatic SCNEC originating from the cervix associated with human papillomavirus (HPV) infection.

Comment 8: Page 4 Line 21: What strain of HPV did the patient have? Please indicate. Also please
Reply 8:

- Thank you very much for your valuable comments but this patient was not tested for HPV strain. We only perform p16 stains, that is a surrogate marker for high-risk HPV infection.
- We have included this issue in the section addressing the limitations.

Changes in the text:

Case Presentation Page 4 Line 21

- These findings were consistent with metastatic SCNEC originating from the cervix associated with human papillomavirus (HPV) infection. [But this patient was not tested for HPV strain.](#)
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Comment 9: Page 5 Line 2: what are the guidelines for best supportive care? It is not objective for the clinical team to define best supportive care. Please restate as “after supportive care was initiated”.

Reply 9:

- Thank you very much for your valuable comments.
- We have revised these according to your suggestions by remove the word “best”.

Changes in the text:

Page 5 Line 2

She died 2 months after [supportive care](#) was initiated.

Page 2 Line 2

after the initiation of [supportive care](#).

Comment 10: Page 5 Line 8: Please indicate, there are only a few case reports of cases of metastatic SCNEC from cervix to breast

Reply 10:

- Thank you very much for your kind and valuable comments. These actually make our manuscript very much improved.
- We have revised these according to your suggestions.

Changes in the text: Page 5 Line 8

therefore, there are only a few [case reports of cases of metastatic SCNEC from cervix to breast](#).

Comment 11: Page 7 Line 8: Please remove best

Reply 11:

- Thank you very much for your valuable comments.
- We have revised these according to your suggestions by remove the word “best”.

Changes in the text: Page 7 Line 8

Therefore, [supportive care](#) was initiated, and she died 2 months later.

Comment 12: [Page 7](#) [Page 11](#): Please improve photo quality for Figure 2

Reply 12:

- Thank you very much for your valuable comments.
- We have improved the quality for Figure 2.

Changes in the text:

improved quality for Figure 2.

Reviewer B

I agree with your diagnosis, but there are a few things I would like to point out in your description.

- Thank you very much for your kind and valuable comments. These actually make our manuscript very much improved.

Comment 1: [Page 4 line 16](#): These tumor cells were positive for cytokeratin (CK), AE1/AE3,... => AE1/AE3 immunostaining is one of several methods for detecting cytokeratin. The description here makes it sound like you tested for cytokeratin and AE1/AE3 separately, if so, please describe the antibody you used to detect cytokeratin and if you used AE1/AE3 antibody to detect cytokeratin, please describe it to avoid confusion.

Reply 1:

- Thank you sincerely for bringing this matter to my attention.
- In this case, we tested AE1/AE3, which is a pan-cytokeratin and contains low-molecular weight and high molecular weight cytokeratin. AE1/AE3 detects intermediate filaments and help to identify epithelial in origin.
- For correction this word, we have revised these according to your insightful comment.

Changes in the text:

Page 1 [line 21](#)

positive for [pan-cytokeratin \(AE1/AE3\)](#)

Page 4 [line 16](#)

The tumor cells were positive for [pan-cytokeratin \(AE1/AE3\)](#).

Comment 2: [Page 5, Line 7](#): SCNEC originating from the cervix as the primary site is extremely rare; therefore, there are only a few published case reports

=> I agree that uterine cervical SCNEC is a rare tumor, but I don't think it's very rare. For example, a recently published paper based on data from the US SEER database included 495 cases of cervical SCNEC patients (Curr Oncol. 2022 Oct 6;29(10):7461-7469). And I personally have seen two or three cases in the last year alone.

Reply 2:

- Thank you very much for your valuable comments.
- We have revised these according to your suggestions by remove the word “extremely”.

Changes in the text: Page 5 Line 7-8

SCNEC originating from the cervix as the primary site is [rare](#).

Comment 2: Page 5, Line 11: Breast cancer is the most frequently diagnosed cancer in women
=> I think this may be different in different countries, but it's true on a global basis. If you're referring to a global basis, I think it's better to write so and add a reference (Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024; 74(3): 229-263. doi:10.3322/caac.21834).

Reply 2:

- Thank you very much for your valuable comments.
- We have revised these and added a reference following your suggestions.

Changes in the text: Page 5, Line 11

- Breast cancer is the most frequently diagnosed cancer in women, [on a global basis](#).
- Reference: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024; 74(3): 229-263. doi:10.3322/caac.21834

Comment 3: Page 6, Line 10: Immunohistochemical staining was positive for AE1/AE3 (epithelial marker), and synaptophysin and chromogranin (neuroendocrine markers), and negative for p16 and CK5/6 (squamous cell carcinoma markers).

=> P16 was described as positive in the previous description (page 4, line 16) and in Figure 2. You probably wrote p63 incorrectly.

Reply 3:

- Thank you very much for your valuable comments.
- We have corrected our text according to your suggestions.

Changes in the text: Page 6, Line 10-11

Immunohistochemical staining was positive for AE1/AE3 (epithelial marker), and synaptophysin and chromogranin (neuroendocrine markers), and negative for [p63](#) and CK5/6 (squamous cell carcinoma markers).

Comment 4: Figure 2 The quality of the photographs is quite unsatisfactory.

Reply 4:

- Thank you very much for your valuable comments.
- We have improved the quality for Figure 2.

Changes in the text:

improved quality for Figure 2.

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